REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Applicants thank the Examiner for the careful examination of this case, and respectfully request reexamination and reconsideration of the case, as amended.

Applicants are submitting the present Amendment without prejudice to the subsequent prosecution of claims to some or all of the subject matter which might be disclaimed by virtue of this paper, and explicitly reserve the right to pursue some or all of such subject matter, in Divisional or Continuation Applications.

Below Applicants address the rejections levied in the Office Action, and explain why the rejections are not applicable to the pending claims as amended.

I. CLAIM STATUS AND AMENDMENTS

Claims 1-2 and 4-15 are pending in this case and stand rejected.

Claims 1, 2, 4-6, 8, 10, and 13-15 are amended. Support for the amendments can be found throughout the specification and in the claims. No new matter has been added.

Claim 1 has been amended to specify that the combination product comprising the positive oil-in-water emulsion and the antibody is used for delivery of a pharmacologically active substance, and that the active substance is incorporated in the emulsion. Support can be found throughout the application, as filed, in particular in paragraphs [0036] to [0039] of the published application, as well as in Claim 6, as filed.

Claim 1 and dependent Claim 14 have been amended to replace the term "compound" with "cationic lipid" to be consistent throughout the claims.

Claim 4 has been amended to correct its dependency.

Claim 6 has been amended to recite that the pharmacologically active substance is incorporated in the oily core of the colloidal particles of the emulsion. Support can be found throughout the application, as filed, in particular at the end of paragraph [0038] of the published application.

Other minor editorial revisions have been made to improve the language therein to better conform to U.S. claim form. Such revisions are non-substantive and not intended to narrow the scope of protection. The revisions include: revising the claims to recite "oil in water emulsion", "at least one

cationic lipid", "heterobifunctional linker", and "combination product" rather than "emulsion", "cationic lipid", "linker", and "product", respectively, to provide proper antecedent basis throughout; replacement of the term "colloid particles" by the term "colloidal particles" in Claim 5 to render the claim more consistent; revising the format of claim 1 to better delineate the components of the claimed combination product; and revising claims 8, 10 and 12 to use proper Markush style format for reciting alternatives.

No new matter has been added by the above amendments.

II. CLAIM OBJECTION

The Office has objected to Claim 4 under 37 C.F.R. § 1.75(c) as being in improper form because it is dependent on Claim 3, which was previously cancelled. See Item 12 on page 3 of the Official Action. In reply, the dependence of Claim 4 has been corrected, thereby obviating the objection.

III. INDEFINITENESS REJECTIONS

The Office has rejected Claim 1 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention for the reasons in Item 14 on page 4 of the Official Action. In particular, the Office indicated that Claim 1 recites the limitation "said compound", for which there is insufficient antecedent basis.

In reply, Claim 1 has been amended to replace "said compound" with "said cationic lipid" for which there is clear antecedent support in the claim. Thus, this amendment obviates the rejection and it should be withdrawn.

IV. OBVIOUSNESS REJECTION

The Office rejected Claims 1-2 and 4-15 under 35 U.S.C. § 103(a) as being unpatentable over KADOUCHE (US 2002/0106324 A1) in view of SINGH et al. (Cancer Letters, 1994, 84: 15-21) for the reasons in Item 16 on page 4 of the Official Action. This rejection is respectfully traversed.

The Office indicated that KADOUCHE teaches a monoclonal antibody coupled to a liposome-type vector, to a cationic-type emulsion or to a cationic lipid. The Office further asserted that SINGH teaches monensin liposomes linked to tumor specific monoclonal antibodies with full retention of immunoreactivity. According to the Office, "it would have been obvious to one of ordinary skill in the art at the time the

invention was made to make a product with a monoclonal antibody coupled to a liposome-type vector, a cationic-type emulsion, or a cationic lipid, as suggested by KADOUCHE, combine it with the monensin liposomes linked to tumor specific monoclonal antibodies with full retention of immunoreactivity, as suggested by SINGH and produce the instant invention".

Applicants respectfully disagree and submit that the Office has failed to show that the prior art references teach, suggest or make obvious all of the claim limitations of claim 1 (*i.e.*, the sole independent claim), as required to support a *prima facie* case of obviousness for the reasons set forth below.

First, Applicants submit that combination of the teachings of KADOUCHE and of SINGH would not have led one skilled in the art, at the time the invention was made, to produce the combination product of claim 1.

Specifically, claim 1 relates to a new system for the delivery of a drug (*i.e.*, a pharmacologically active substance) to a specific target within the mammalian body. The claimed drug delivery system comprises an antibody covalently linked to an oil-in-water emulsion, wherein the drug of interest is incorporated in the emulsion. This is reflected in independent claim 1, as amended, which recites a combination product for the delivery of a pharmacologically active substance, said

combination product comprising a positive oil-in-water emulsion and an antibody, wherein said emulsion comprises, at the oil-water interface, at least one cationic lipid selected from the group consisting of a C_{10}-C_{24} alkylamine, a C_{10}-C_{24} alkanolamine and a cholesterol ester, wherein said cationic lipid is linked to said antibody by a heterobifunctional linker, and wherein the pharmacologically active substance is incorporated in the emulsion.

KADOUCHE teaches that an antibody (more particularly, an anti-ferritin monoclonal antibody) may be coupled to a liposome-type vector, a cationic-type emulsion or a cationic lipid, which may, optionally, carry a drug (see paragraph [0064]). KADOUCHE does not teach how to couple the antibody to the carrier (*i.e.*, liposome, emulsion or lipid) of the drug.

SINGH describes a system for the delivery of a potentiator of a drug, *i.e.*, a compound whose administration, in combination with a drug of interest, enhances or increases the biological effect or activity of the drug. More specifically, SINGH provides a system for the delivery of monensin, a potentiator of ricin A immunotoxins. In this system, monensin is encapsulated in liposomes that are covalently linked, *via* a heterobifunctional linker, to tumor specific monoclonal antibodies. SINGH shows that these monoclonal antibody targeted

monensin liposomes, when incubated *in vitro* in combination with a ricin A immunotoxin, are more potent than monensin liposomes or monensin in buffer at potentiating the cytotoxicity of the immunotoxin (see Figure 4 and paragraph 3.4 on page 19). However, such a teaching in no way suggests a positive oil-in-water emulsion, wherein the emulsion includes at least one cationic lipid selected from the group consisting of a C_{10}-C_{24} alkylamine, a C_{10}-C_{24} alkanolamine and a cholesterol ester, wherein the antibody is covalently linked to the cationic lipid by a heterobifunctional linker as in claim 1.

Therefore, Applicants respectfully submit that KADOUCHE or SINGH, taken alone or in combination, does not teach, suggest or make obvious a drug delivery system composed of an antibody coupled to a positive oil-in-water emulsion, wherein the emulsion includes at least one cationic lipid selected from the group consisting of a C_{10}-C_{24} alkylamine, a C_{10}-C_{24} alkanolamine and a cholesterol ester, wherein the antibody is covalently linked to the cationic lipid by a heterobifunctional linker, and wherein the emulsion incorporates the drug to be delivered as required by independent claim 1.

The Office states that one of ordinary skill in the art would have been motivated to combine the teachings of the cited references to arrive at the claimed invention, "because

SINGH discloses that monoclonal antibody targeted monensin liposomes were 100 times more potent than monensin liposomes in potentiating the activity of ricin A immunotoxin against various tumor cell lines *in vitro*".

Applicants respectfully disagree and submit that the positive effects on the potentiating ability of a potentiator, which results from encapsulation of the potentiator in antibody targeted liposomes, are not predictive of the effects that such an encapsulation would have on the activity of a drug. Moreover, the effects of encapsulation in targeted liposomes on the potentiating ability of a potentiator are even less predictive of the effects of encapsulation in a targeted emulsion on the activity of a drug. This is all the more true given that SINGH does not provide any explanation for the observed increase in potentiation. On the contrary, SINGH (1) admits that the mechanism of action of monensin is sill quite unclear (this correlates to an unpredictable art) (2) proposes that liposomal monensin could be taken up by the cells to a greater degree, especially if it is tumor targeted, but (3) notes that experiments carried out *in vivo* have shown that the activity of ricin was significantly increased by co-administration of monensin liposomes that were NOT tumor targeted (see last paragraph of first column and first paragraph

of second column on page 20). Thus, there is no reasonable explanation in SINGH for the observed increase in potentiation. Moreover, it suggests that the teaching in SINGH relates to an unpredictable art field. As such, Applicants respectfully submit that SINGH is not predictive for using an emulsion type system as in claim 1 of the instant application.

It is well established that a rationale to support a conclusion that a claim would have been obvious is that all the claimed elements were known in the prior art and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions. Obviousness also requires a reasonable expectation of success, which means that the combination of cited references would have yielded nothing more than predictable results to one of ordinary skill in the art. *See, KSR International Co. v. Teleflex Inc.*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1395 (2007); and M.P.E.P. § 2143.02. The mere fact that references can be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *See, KSR*, 550 U.S. ___, ___, 82 USPQ2d 1385, 1396 (2007), and M.P.E.P. § 2143.01, III.

Based on the above, it is respectfully submitted that combining the teachings of KADOUCHE and SINGH would not yield

predictable results, let alone arrive at the present invention. For this reason, the combination of KADOUCHE and SINGH do not render obvious the claimed invention.

Furthermore, Applicants submit that SINGH actually teaches away from using an emulsion type system. It is well established that prior art references cannot be combined where a reference teaches away from their combination. *See*, M.P.E.P. § 2145, X, D, 2. In this regard, SINGH mentions that "attempts to improve the delivery of monensin has been approached by conjugating it to human serum albumin [...] or as a lipid-water emulsion [...] leading to limited success *in vivo*". [Emphasis added). See page 15, last two lines to page 16, first two lines of the SINGH.

Therefore, Applicants respectfully submit that those skilled in the art, at the time the invention was made, would not have been motivated to combine the teachings of KADOUCHE and SINGH, and even if they were, they would not have been motivated to couple an antibody to an emulsion to develop a targeted drug delivery system given the teaching away in SINGH.

At the very least, the above-noted passage is furterh evidence of the unpredictable nature of the teaching in SINGH. Thus, the combining the teachings of KADOUCHE and SINGH would

not yield predictable results as is required to establish a *prime facie* case of obviousness.

In light of the above, Applicants respectfully submit that neither KADOUCHE nor SINGH, taken alone or in combination, teaches, suggests or makes obvious each and every element of independent Claim 1. For this reason, Claim 1 is novel and unobvious over the combined prior art references.

Claims 2 and 4-15, directly or indirectly, depend on independent Claim 1. Accordingly, Claims 2 and 4-15 are also novel and unobvious over the combined prior art references in view of their dependency on Claim 1.

Therefore, Applicants respectfully submit that the above 103(a) obviousness rejection is untenable and should be withdrawn.

V. CONCLUSION

Applicants again thank the Examiner for the careful review of this case. The claims have been amended to obviate all rejections. Based on the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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